RESEARCH ARTICLE

Accuracy of Sentinel Node in Detecting Lymph Node Metastasis in Primary Endometrial Carcinoma

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Abstract

Background: Endometrial carcinoma is the most common gynecological cancer and its treatment is still controversial, especially in its early stages. There are conflicting data about the efficacy of retroperitoneal lymphadenectomy during abdominal hysterectomy and bilateral salpingoophrectomy treatment. Lymphadenectomy carries a risk of severe complications, especially in women with co-morbidities. Selective lymphadenectomy has been widely employed for staging evaluation of endometrial carcinoma because it is simple and seems to provide reliable data regarding nodal metastasis. This study was designed to evaluate accuracy of sentinel node sampling in detecting lymph node metastasis in primary endometrial carcinoma during staging laparotomy. Materials and Methods: Ninety-three women with endometrial carcinoma at high-risk for nodal metastasis were studied. During laparotomy, methylene blue dye was injected into sub-serosal myometrium, then retroperitoneal spaces were opened and blue lymph nodes within pelvic and para-aortic regions were removed as separate specimens for histopathological examination (sentinel lymph nodes = SLNs). Hysterectomy and selective lymphadenectomy then performed for all women included in this study. Results: Deposition of methylene dye into at least one lymph node was observed in 73.1% (68/93) of studied cases. 18.3% (17/93) of studied women had positive lymph node metastasis and 94.1% (16/17) of them had positive metastasis in SLNs. In this study, SNLs had 94.4% sensitivity and 100% specificity in prediction of lymph node metastasis. Mean number of lymph nodes removed from each case decreased when SLNs biopsy were taken. Conclusions: SLNs are the key lymph nodes in endometrial tumor metastasis and their involvement could be an indicator for whether or not complete systematic lymphadenectomy is needed during staging laparotomy.

Keywords: Sentinel lymph node - endometrial - carcinoma - lymph nodemetastasis - prediction

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Introduction

Endometrial carcinoma is the most common gynecological cancer and treatment of endometrial carcinoma is still controversial especially in its early stages (Cetinkaya et al., 2014; SGO Clinical Practice Endometrial Cancer Working Group et al., 2014).

FIGO staging of endometrial cancer revised in 2009 to include lymph node status as one of the most important prognostic factors in women with endometrial cancer (Haltia et al., 2014).

Still there is conflicting data about retroperitoneal lymphadenectomy during abdominal hysterectomy and bilateral salpingoophrectomy treatment of endometrial carcinoma and to what extent lymphadenectomy should be performed (Ilker et al., 2015). Advocates demonstrate that omitting lymphadenectomy exposes women with early-stage disease (80% of endometrial cancer) to risk of recurrence due to inadequate initial staging (Kafshdooz et al., 2014).

Others argue that lymphadenectomy carries a risk of severe complications such as lymphedema or lymphocyst formation, especially in women with endometrial cancer, who often have comorbidities such as obesity, hypertension and diabetes (Aksoy et al., 2014), and, lymphadenectomy is not necessary in women at low risk of lymph node involvement (stage 1a-1c), (Christopher et al., 2008).

Selective lymphadenectomy has been widely employed for staging evaluations of endometrial carcinoma because it is simple and seems to provide reliable data regarding true incidence of nodal metastasis (Baser et al., 2013).

SLN is the first node receiving lymphatic drainage from primary tumor and pathological status of SLN should therefore reflect the overall status of entire lymphatic basin. Thus, a patient with negative SLN for metastasis may managed by SLN biopsy instead of a systemic lymphadenectomy (Krusun et al., 2014).

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American Society of Breast Surgeons recommended a false-negative rate of 5% or less in order to abandon axillary dissection and Kang and colleagues suggests that a false-negative rate ≤2% should be a goal for determining clinical usefulness of preoperative or intraoperative prediction models for low-risk of nodal metastasis (Kang et al 2012).

This study designed to evaluate the accuracy of SLN biopsy in detecting lymph nodes metastasis in primary endometrial carcinoma during staging laparotomy.

Materials and Methods

Based on previous study published on PubMed before 2007 regarding SLNs and using G* Power software version 3.17 for sample size calculation (*Heinrich Heine Universitat; Dusseldorf; Germany), setting -error probability at 0.05, power (1- error probability) at 0.95 % and effective sample size (w) at 0.3. The effective size (w) was calculated as follows: , where X^2 is the chi-square test and N is the total sample size. After assuming 10% drop rate, the minimal number of participants needed to produce a statistically acceptable figure was 88 women.

Ninety- three women with histologically proven endometrial carcinoma (documented by endometrial biopsy) and judged to be at risk for nodal metastasis on the basis of high grade (2 or 3) or advanced stage (II, III or IV) included in this study which conducted in Ain Shams University Maternity Hospital and Egyptian Cancer Institute, from May 2007 to May 2011.

All women included in this study after approval of study protocol from the ethical committee from both institutes and after informed written consent explaining the surgical procedure, possible intra-operative and post-operative complications.

None of studied women had previous treatment or surgeries related to current endometrial carcinoma or signs or symptoms suggesting distant metastasis, also, none of studied women had adnexal masses or enlarged pelvic or para-aortic lymph nodes detected by either bimanual examination or preoperative investigations done for staging.

Women with ovarian mass discovered by preoperative abdominal ultrasound or computerized tomography scan or with sensitivity to methylene blue dye confirmed by preoperative skin sensitivity test were excluded from this study.

After exploration of abdomen and obtaining pelvic washings for cytology, uterus and fallopian tubes were hold by straight clamps to occlude fallopian tubes. Methylene blue dye then injected at all possible locations of the tumor and in midline using a tuberculin syringe. 1 ml of methylene blue dye (1%) was injected into sub-serosal myometrium at 3 sites; most superior portion of uterine fundus, anterior and posterior midline 2 cm below the superior injection site. Trans-peritoneal dye uptake monitored for 10 minutes after injection. Locations and routes of the visualized lymphatic channels noted and marked on an anatomic diagram. Retroperitoneal spaces then opened to expose major pelvic vessels and lymph nodes. Lymphatic vessels taking blue color dissected in an effort to identify dye-containing lymph nodes. Dye-containing lymph nodes identified, removed and forwarded to pathology assessment and examination as individual specimens (SLN). Locations of all dye-containing nodes recorded on an anatomic diagram. Dissection along abdominal aorta to level of renal arteries was not attempted. After SLN biopsies, an extra-fascial hysterectomy and bilateral salpingoophrectomy performed. Exploratory operative staging procedure also includes a partial omentectomy, pelvic and para-aortic lymphadenectomy. Extent of lymphadenectomy was decided by senior surgeon intra-operatively depending on grade of tumor, depth of invasion, size, location of endometrial carcinoma and patient`s fitness to such risky intervention. Selective pelvic lymphadenectomy involves removal of lymphatic tissue from both anterior and medial surfaces of iliac vessels and from obturator fossa above level of obturator nerve. Selective aortic lymphadenectomy involves removal of lymphatic tissue below level of inferior mesenteric artery. Para-aortic lymphadenectomy was done in 62 women and the procedure was abandoned as decided by senior surgeon in 31 women (due to marked obesity in 21 women which made the procedure difficult, due to marked intra-abdominal adhesions in 6 women and due to intra-operative bleeding from injured tributary of the internal iliac vein in 4 women). All surgically removed lymph nodes were examined histologically using bivalving protocol, which is a modification of the recent European Organisation for Research and Treatment of Cancer protocol. After sizing and fixation in 10% neutral-buffered formalin for 24 hours, nodes were bivalved longitudinally, approximately into two parts. Two half-nodes embedded in paraffin. All SLNs were step-sectioned at 2 mm intervals; 3-μm thin sections obtained using a microtome with gaps of 50 µm between them. Each 3-μm thin section placed on a microscopic slide and stained with hematoxylin & eosin. All thin sections were histologically evaluated by experienced pathologist who was blinded to patient`s criteria. Negative lymph nodes for metastasis by routine hematoxylin & eosin staining, were stained using immunohistochemistry (IHC) standard avidin-biotin complex technique with an anti-cytokeratin antibody (AE1/AE3, DAKO, Japan) at a 1:500 dilution. Data were collected, tabulated then statistically analyzed using Statistical Package for Social Sciences (SPSS); computer software version 18 (Chicago, IL, USA). Numerical variables were presented as mean and standard deviation (±SD), while categorical variables were presented as number (n) and percentage (%). Statistical analysis performed by univariate χ^2 tests and multivariate logistic regression for odds ratios to identify independent factors predicting false negative results. A difference with p value <0.05 was considered statistically significant. Variables included; body mass index (BMI), depth of myometrium invasion, tumor grade, FIGO stage, palpable lymph nodes. SLN identification rate is the percentage of patients in which at least one SLN identified.

Sensitivity: is the proportional detection of individuals with the disease of interest in the population. Specificity: is the proportional detection of individuals without the disease of interest in the population. Positive Predictive

Value (PPV): is the proportion of all individuals with positive tests, who have the disease. Negative Predictive Value (NPV): is the proportion of all individuals with negative tests, who are non-diseased.

Results

Ninety-three women with endometrial carcinoma, were included in this study, mean age of studied women was 56.34 ± 10.03 years (range 33-80), mean BMI was 29.58 ± 7.293 kg/m^2 (range18 -45), 43% (40/93) of studied women were diabetics and 36.5% (34/93) were hypertensive. Table 1

Five minutes after injection of methylene blue dye, all bilateral uterine lymphatic vessels and lymphatic drainage of the uterus seen. Superficial fine vessels were usually identified by a bright blue ''*flush*'' during injection, larger lymphatic vessels could be identified along ovarian vessels and within broad ligaments 5-10 minutes after dye injection. Dye within lymphatic vessels easily seen after division of round ligaments on both sides and in some cases, gentle dissection along visualized lymphatic channels led to an obvious blue stained lymph node.

Total of 1322 lymph nodes were removed from 93 studied women, mean number of lymph nodes removed from each cases was 14.2±2.3 nodes (range 7-24), which, was increased to 17.25±3.33 when para-aortic lymphadenectomy was done, and, it was decreased to 11.58±3.56 when para-aortic lymphadenectomy was omitted. All resected lymph nodes examined by hematoxylin and eosin staining and when negative lymph nodes examined by immunohistochemistry, no new lymph nodes metastasis detected.

Final pathology report showed; 81.72% (76/93) of studied women had negative nodal metastasis and 18.28% (17/93) of studied women had positive nodal metastasis (12 with macro-metastases, 5 with micro-metastases (defined as a single focus of metastatic disease per node, measuring between 0.2-2 mm).

Fourteen% (13/93) women with grade 1, 70% (65/93) women with grade 2 and 16% (15/93) women with grade 3 endometrial carcinoma were included in this study. Table 1

The relation between lymph node metastasis and histopathological type of studied cases of endometrial carcinoma was statistically insignificant. Table 1

17.2% (16/93) women with endometrioid adenocarcinoma had lymph node metastasis, 1.07% (1/93) women with clear cell carcinoma had lymph node metastasis and 0% (0/93) women with papillary serous carcinoma had lymph node metastasis. Table 1

There was no significant relation in this study between rate of SLN detection and either tumor grade or FIGO staging of studied cases. Table 2 and 3

In addition, there no significant relation between rate of SLN detection and histological type of studied cases. Table 4

Table 1. Demographic data of Studied Women

Variables	Negative lymph nodes (Number 76)	Positive lymph nodes (Number 17)	P Value
Age (years)	54.32 ± 11.5	58.36 ± 8.56	0.326 (P>0.05)
Parity	4.31 ± 2.92	4.13 ± 2.89	0.407 (P>0.05)
BMI (Kg/ m2)	28.42 ± 7.212	30.74 ± 7.305	0.398 (P>0.05)
Comorbidities			
Diabetes mellitus	37 (39.7%)	3 (3.22%)	0.259 (P>0.05)
Hypertension	24 (25.8%)	10 (10.75%)	0.259 (P>0.05)
Grades of endometrial carcinoma			
Grade 1	13 (14%)	0 (0%)	0.387 (P>0.05)
Grade 2	53 (57%)	12 (13%)	0.387 (P>0.05)
Grade 3	10 (10.7%)	5 (5.3%)	0.387 (P>0.05)
FIGO Staging			
Stage I	46 (49.4%)	9 (9.67%)	0.219 (P>0.05)
Stage II	22 (23.65%)	2 (2.1%)	0.219 (P>0.05)
Stage III	8 (8.6%)	6 (6.45%)	0.219 (P>0.05)
Stage IV	0 (0%)	0 (0%)	0.219 (P>0.05)
Histo-pathological results			
Endometroid adenocarcinoma	71 (76.3%)	16 (17.2%)	0.441 (P>0.05)
Clear cell carcinoma	3 (3.22%)	1 (1.07%)	0.441 (P>0.05)
Papillary serous	2 (2.1%)	0 (0%0)	0.441 (P>0.05)

Table 2. Relation between Sentinel Lymph Node Detection (SLN) and Tumor Grade

Grades of endometrial Carcinoma	Sentinel lymph nodes detected		Total	Detection rate
	Positive	Negative		
Grade 1	7	6	13	53.84%
Grade 2	48	27	65	73.83%
Grade 3	13	2	15	86.66%
P value	P >0.05 (non-significant)		93	

Table 3. Relation between Sentinel Lymph Node Detection (SLN) and FIGO Staging

FIGO Staging	Sentinel lymph nodes detected		Total	Detection rate
	Positive	Negative		
IA	5	4	9	55.55%
IB	18	11	29	62.06%
IC	12	5	17	70.58%
IIA	14	2	16	87.50%
IIB	7	1	8	87.50%
IIIA	10	2	12	83.30%
IIIB	2	0	2	100%
P value	P >0.05 (non-significant)		93	

Table 4. Relation between Sentinel Lymph Node Detection (SLN) and Histological Type of Endometrial Cancer

Histological type of endometrium carcinoma	Sentinel lymph nodes detected		Total	Detection rate
	Positive	Negative		
Endometrioid adenocarcinoma	70	17	87	80.45%
Clear Cell Carcinoma	2	2	4	0%
Papillary serous carcinoma	0	2	2	50%
P value	P >0.05 (non-significant)		93	

Most of the studied women experienced greenish or greenish-blue discoloration of their urine and nails, which persisted for average of 24 hours after surgery. Post-operative prolonged ileus were recorded in 8.6% (8/93), which managed conservatively and wound sepsis in 7.5% (7/93) women managed by secondary closure after antibiotic course according to culture and sensitivity and wound debridement.

Intra-operative complications recorded in 1.075% (1/93) women in form of anaphylactic reaction to methylene dye in spite of negative pre-operative skin sensitivity test (diagnosed by bronchospasm and dropped oxygen saturation to 60% under anesthesia). In addition; intra-operative bleeding recorded in six (6.45%) women due to bleeding from tributaries of external iliac vein and managed by compression and transfusion of packed RBCs.

Discussion

FIGO staging of endometrial cancer was revised in 2009 to include lymph node status as one of the most important prognostic factors and recommended lymphadenectomy as an important step during surgical staging of endometrial cancer, however, the appropriate criteria for lymph node assessment have not been established (Tangjitgamol et al., 2013).

Although, complete pelvic and para-aortic lymphadenectomy is still recommended by many gynecologic oncologic societies and guideline committees (ACOG, 2005; Creasman et al., 2006 Greer et al., 2009), medical Research Council ASTEC trial, suggested that there was no benefit for performing systemic lymphadenectomy for early stage endometrial cancer on patient`s survival or prevention of recurrence and non-invasive assessment of lymph node status to target specific lymph nodes for sampling is more beneficial than complete pelvic and/or para-aortic lymphadenectomy (ASTEC study group., 2009).

This study designed to assess the accuracy of SLN biopsy in detecting lymph nodes metastasis in women with primary endometrial carcinoma during staging laparotomy. Two aspects, mapping success rates and mapping accuracy, determine effectiveness of lymphatic mapping and SLNs biopsy.

Mapping success rate reflects the ability to identify SLN. Mapping accuracy is the false-negative rate, which defined as women with node metastasis in-spite of negative SLN for metastasis (Bass et al., 1999). In this study, uptake of dye demonstrated in 222 lymph nodes and mean number of SLN removed 3.26±1.4 (range 1-6). Deposition of dye into at least one SLN was observed in 73.1% (68/93) cases and SLN could be identified in one side of pelvis in 44.1% (30/68) cases, while, SLN could be identified in both sides of the pelvis in 55.9% (38/68) cases.

Altgassen et al, reported 92% detection rate of SLN (Altgassen et al., 2007), and, Delaloye et al, reported 100% detection rate of SLN when both a radioactive tracer and blue dye were injected hysteroscopically into the sub-endometrial layer beneath the tumor (Delaloye et al., 2007).

SLN detection rates recorded by Burke et al, Holub et al and Gien et al, were 61.5%, 67% and 56%; respectively (Burke et al., 1996; Holub et al., 2002; Gien et al., 2005).

Although, Echt et al, failed to identify any SLN in their series of 8 patients (Echt et al., 1999), Holub and colleagues, identified SLN in 61.5% of their cases when blue dye was injected into the fundus and in 83% of their cases when dye was injected into uterine cervix and fundus (Holub et al., 2002).

Other authors recorded 100% detection rate of SLN when dye injected in the uterine cervix in women with endometrial carcinoma (Gargiulo et al., 2003; Barranger et al., 2004).

While, Frumovitz et al, stated that injection of dye into the uterine cervix, fundus or both, maps uterus and its sentinel nodes rather than tumor and its lymphatic channels (Frumovitz et al., 2007).

The most physiologic way to detect SLN is the peri-tumoral application of tracer or dye and since histological studies demonstrate that the submucosal lymphatic plexus drains into subserosal plexus, a subserosal tracer application might identify the lymphatic drainage appropriately (Altgassen et al., 2007).

In 72.1% (49/68) of studied cases SLN were found in the medial group of external iliac lymph nodes (inter-iliac group) and in 20.6% (14/68) cases SLN were found in the lateral group of external iliac lymph nodes, while, in 7.3% (5/68) cases SLN were detected in the obturator lymph nodes. No stained lymph nodes detected in hypogastric, common iliac or para-aortic lymph nodes.

Several studies identified SLN in the para-aortic area, with or without associated SLN in pelvis, which confirms spread patterns of endometrial cancer (Creasman et al., 1987; Mariani et al., 2001; Niikura et al., 2004; Raspagliesi et al., 2004; Maccauro et al., 2005).

SLN was not detected in the para-aortic region in Ballester et al, and Krusun et al, studies (Ballester et al., 2011; Krusun et al., 2014), also, Jobo et al, found that lymphatic metastasis occurred more frequently via hypogastric and obturator lymph nodes, while direct para-aortic spread was rarely observed (Jobo et al., 2005).

Mariani et al, concluded that isolated para-aortic nodes involvement occur in 1-6% of endometrial carcinoma, while, common and external iliac nodes are the key nodes in metastasis and their involvement indicates the need for systematic lymphadenectomy (Mariani et al., 2001).

Conversely, Burke et al, suggested lymphatic pathways traveling through infundibulopelvic ligament directly to para-aortic lymph nodes (Burke et al., 1996).

Mean number of SLN removed in this study was 3.26 ± 1.4 (range 1-6), and, mean number of SLN detected was 2.6 (range 1-4) in Barranger et al study, 2.6 (range 1-5) in Ballester et al study and 3.7 (range 1-9) in Niikura et al, study (Barranger et al., 2005; Niikura et al., 2007; Ballester et al., 2011).

18.28% (17/93) women found to have positive lymph node metastasis in this study, 94.1% (16/17) of them had positive metastasis in SLN and in 5.9% (1/17) of them SLN could not be detected. In this study, sentinel lymph node had 94.4% (17/17+1) sensitivity, 100% (86/86+0) specificity, 100% PPV (17/17+0) and 98.9% NPV (86/86+1).

Mean number of lymph nodes removed from each case was 14.2±2.3 node, which decreased to 3.26 ± 1.4 when SLNs biopsy taken, the use of SLN technique would limit the extensive lymph nodes dissection during staging laparotomy of endometrial carcinoma. Burke et al, found that microscopic nodal metastasis to SLN identified in 2-4 women with proven lymphatic spread (Burke et al., 1996).

Altgassen et al, found nodal metastasis in 14.28% (3/21) cases, 2 had SLN with metastatic disease which reflected accurately and correctly the status of pelvic lymphatic basin and one had sentinel node free of metastatic disease with metastasis in pelvic lymph nodes (62.5% sensitivity of SLN), (Altgassen et al., 2007).

Ballester et al, found that 25% (10/40) women in whom at least one positive SLN, nine out of 10 with positive SLN had no non-sentinel nodes metastasis, while, one out of 10 with positive SLN had two non-sentinel nodes metastasis and none of women with negative SLN had a positive non-SLN metastasis (no false-negative cases), (Ballester et al., 2011).

The sensitivity and specificity of SLN in detection of lymph node metastasis were 100% in Niikura et al studies (Niikura et al., 2004). Frumovitz et al, did not find any metastatic disease in either sentinel or non-sentinel lymph nodes detected in 18 cases of endometrial carcinoma (Frumovitz et al., 2007). Mapping success rate reflects the ability to identify SLNs. Mapping accuracy is the false-negative rate, which defined as women with node metastasis in-spite of negative SLN for metastasis.

False negative rate is particularly important, as it potentially serve as a secondary source of malignant seeding affecting patients' survival (Bass et al., 1999).

In this study, one case had lymph node metastasis without SLN metastasis. The histological diagnosis of this case was clear cell carcinoma. This indicate that clear cell carcinoma may have different lymphatic spread map and had high potential for metastasis than endometrioid adenocarcinoma. Systemic lymphadenectomy should done in patients with clear cell carcinoma even if they did not have SLN metastasis. Although, many authors concluded that SLN had 0% false-negative rates, a limited number of patients were included in their published studies (8-28 patients), (Pelosi et al., 2003; Fersis et al., 2004; Lelievre et al., 2004; Niikura et al., 2004; Raspagliesi et al., 2004; Maccauro et al., 2005).

Since, statistical analysis based on the number of node-positive patients and because of low incidence of lymph node metastasis in early-stage endometrial cancer, a large population based studies needed in order to calculate properly the clinical sensitivity and false negative rates of SLN technique.

This study concluded that SLN are the key lymph nodes in tumor metastasis and their involvement could be an indicator for lymph node metastasis and as indicator whether complete systematic lymphadenectomy needed or not during staging laparotomy.

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